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DNA Repair: Lessons from the Evolution of Ionizing-Radiation-Resistant Prokaryotes – Fact and Theory

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1. Introduction

At the outset, I believe that the concept of ionizing-radiation (IR) resistance needs to be clarified in a tangible manner for readers of this chapter. I propose the following general definition adopted in a previous paper (Sghaier et al., 2008): An ionizing-radiation-resistant prokaryotes (IRRP) is any vegetative prokaryote that can thrive after exposure to high, acute IR (generally, with a D_{10} value - the dose necessary to effect a 90% reduction in Colony Forming Units - greater than 1 kGy) using efficient physiological, genetic and proteic protection and repair mechanisms to fully amend its DNA DSBs. IR resistance has been observed in a broad range of prokaryotic groups (Kopylov et al., 1993), including hyperthermophilic Archaea (*P. abyssi*, *P. furiosus*, *Thermococcus marinus*, *Thermococcus radiotolerans* and *Thermococcus gammatolerans*) (DiRuggiero et al., 1997; Jolivet et al., 2003a; Jolivet et al., 2003b; Jolivet et al., 2004), halophilic Archaea (*Halobacterium* sp.) (Kottemann et al., 2005), the *Deinococcus-Thermus* group (many *Deinococcus* sp. and *Truepera radiovictrix*) (Albuquerque et al., 2005), Actinobacteria (*Rubrobacter radiotolerans*, *Rubrobacter xylanophilus* and *Kineococcus radiotolerans*) (Yoshinaka et al., 1973; Ferreira et al., 1999; Phillips et al., 2002; Chen et al., 2004), Proteobacteria (*Methylobacterium radiotolerans* and *Acinetobacter radioresistens*) (Ito and Iizuka, 1971; Nishimura et al., 1994), Cyanobacteria (*Chroococcidiopsis* sp.) (Billi et al., 2000), and Sphingobacteria (*Hymenobacter actinosclerus*) (Collins et al., 2000). However, with the exception of *Deinococcus* and *Pyrococcus*, very little information is available regarding the mechanisms of IR resistance and comparative genomics in the above-mentioned prokaryotes. *D. radiodurans* is the current gold-medallist of IR resistance among prokaryotes with a completely sequenced genome (Liolios et al., 2006; Liolios et al., 2010), and can amend more than 100 DSBs per chromosome, induced by IR, without loss of viability (Moseley, 1983; White et al., 1999). After breaking of its 3.2 Mb genome into 20−30 kb pieces by a high dose of IR, *D. radiodurans* fascinatingly reassembles its genome such that 3 hr later fully restructured nonrearranged chromosomes are present (Galhardo and Rosenberg, 2009). Nine interrelated explanations for the extreme IR resistance of *D. radiodurans* have been proposed: (i) the binding of IrrI (DR0171) to genomic repeat sequences that might prevent exhaustive chromosomal degradation after IR exposure - *irr* for IR resistance - (Udupa et al., 1994), (ii) the

RecA(DR2340)-promoted DNA strand exchangeby quite efficient pathways (Kim and Cox, 2002; Sghaier et al., 2010), (iii) the unusual genomic toroidal morphology (Levin-Zaidman et al., 2003) commented in an another paper (Battista et al., 2003), (iv) the prompt PprI/IrrE(DR0167)-induced DNA repair in response to IR stress - *pprI* for inducer of pleiotropic proteins promoting DNA repair - (Earl et al., 2002; Hua et al., 2003; Lu et al., 2009), (v) the critical role played by PprA (DRA0346) in a presumed IR-induced DNA end-joining repair mechanism - PprA for pleiotropic protein promoting DNA repair A - (Narumi et al., 2004), (vi) the divergent evolutionary route of adaptation to IR resistance in comparison to IR-sensitive prokaryotes (IRSP) (Omelchenko et al., 2005; Makarova et al., 2007; Sghaier et al., 2008) including the acquisition of a putative radiation/desiccation response motif (RDRM) and regulon (RDR) (Makarova et al., 2007; Makarova and Daly, 2011), (vii) the stabilization by "holding proteins" of base pairing between closely opposed strand breaks (Cox and Battista, 2005), (viii) the extended synthesis-dependent strand annealing (ESDSA) process, which involves PolA-accomplished DNA synthesis (completed by crossovers achieved by RecA) (Zahradka et al., 2006), with the participation of Pol III and RadA (Galhardo and Rosenberg, 2009; Slade et al., 2009), and (ix) the protein-centered view of IR toxicity (Daly et al., 2007; Daly, 2010; Daly et al., 2010) based on the Mn(II)-facilitated recovery from IR injury (Daly et al., 2004). Yet, why *D. radiodurans* is an extremely IR-resistant bacterium whereas *Escherichia coli* is not is still an open question. For instance, previous literature (Daly et al., 2004; Daly et al., 2007; Daly, 2010; Daly et al., 2010) have suggested that protein protection from damage by oxidation and IR is what makes *D. radiodurans* IR-resistant compared to IRSP including *E. coli*. If so, it raises the question of whether *E. coli* might be able to amend a genome fragmented by restriction enzymes even though it can not amend severe damage induced by IR (Slade et al., 2009), unless it is mutated (Harris et al., 2009).

Interestingly, *D. radiodurans* and *P. furiosus* are able to efficiently repair DSBs in a similar manner (DiRuggiero et al., 1997). In addition, *D. radiodurans* and *P. abyssi* respond in a similar fashion to DNA damage caused by IR (Jolivet et al., 2003b). DNA replication in *D. radiodurans* is known to cease following irradiation (Dean et al., 1966; Moseley and Copland, 1976), which is comparable to the efficient strategy utilized by *P. abyssi* in response to DNA damage that includes an uncoupling of DNA repair and DNA synthesis (Jolivet et al., 2003b). Another shared feature in irradiated *D. radiodurans* and *P. abyssi* is the transport of damaged DNA that should prevent the accumulation of genetic mistakes (Jolivet et al., 2003b). Further study will be necessary to discover mechanistic commonalities among IRRP.

Presently, one of the most significant conclusions that investigators drew by comparing IRRP with IRSP was that the most resistant cells accumulated about 300 times more Mn and about three times less Fe than the most sensitive cells which contributes to protecting their enzymes and the repair functions they catalyze (Daly et al., 2004; Daly et al., 2007; Daly, 2010; Daly et al., 2010). Interestingly, a recent survey of an Fe-rich site in Tunisia (Tamra mine in Nefza) showed relatively high concentrations of Fe (~9.9%) and Mn (~2242 ppm) with a high environmental radioactivity level (~1.5 microsieverts/hour (μSv/h)) nearby the site. In the United States of America (USA), the Ocean Drilling Program, under contract with the National Science Foundation, has recently surveyed environments representative of a broad range of subsurface conditions found in marine sediments (D'Hondt et al., 2004). Among the most striking features of deeply buried sediments (20-100 meters below the sea floor (mbsf)) are Mn-rich sites with high natural γ-radiation levels (see Figure F14 in http://www-odp.tamu.edu/publications/prelim/201_prel/201PREL.PDF and

http://www.ldeo.columbia.edu/BRG/ODP/ODP/LEG_SUMM/201/leg201.html#fig4) (Daly MJ, personal communication, 2006). In this context, anaerobic and hyperthermophilic *Deinococcus* sp. have been isolated from the subsurfaces of hydrothermal vents at depths of 64.8 to 128.9 mbsf, where temperatures range from 76 to 91.4°C (Kimura et al., 2003). This finding supports the possibility of the coexistence within the same ecological niche of *Deinococcus* species and other anaerobic hyperthermophilic archaea.

16 rDNA-based phylogenies place *Deinococcus* very close to hyperthermophiles and the root of the phylogenetic tree, with organisms exhibiting IR resistance forming a scattered group (Woese, 1987; Cox and Battista, 2005). In this context, Cavalier-Smith employed aspects of palaeontology, sequence trees, and the methods of transition analysis and congruence testing to demonstrate that the last universal common ancestor (LUCA) lies within eubacteria; specifically, among negibacteria of the superphylum Eobacteria (Hadobacteria and Chlorobacteria) (Cavalier-Smith, 2006). Several important characters indicate that Hadobacteria, including the genus *Deinococcus*, are more primitive than other phyla, with the exception of Chlorobacteria (Cavalier-Smith, 2006). As far as the dispersed phylogenetic clades of IRRP are concerned, the idea of Cox and Battista (Cox and Battista, 2005) concerning convergent evolution remains possible, but it needs further explanation as to how IR-resistant lineages became similar to each other. An immediate question is whether horizontal gene transfer was involved in the convergent evolution of some pivotal genes essential for IR resistance in IRRP. If so, several different evolutionary scenarios are possible: either the genetic gain consisted of a few relatively large DNA fragments, or the genetic gain included individual genes one-by-one. Additionally, the theory of convergent evolution requires that IRRP responded in a similar fashion to DNA damage caused by IR (DSBs) through adaptation to identical environments under the same driving forces. More interestingly, Cox and Battista raised the possibility that IR resistance could be a vestige of DNA repair systems that were present in ancestral species, and has been retained in those organisms that continue to require this phenotype (Cox and Battista, 2005). Their explanation asserts that most descendents "lost" the ancestor's ability to cope with DNA damage and predicts that the molecular mechanisms of IR resistance should be similar among IR-resistant species. Given new insights from pertinent organisms, novel comparative analytical tools, and extensive phylogenetic endeavours, it should soon be possible to test current and future hypotheses concerning the origin of IRRP (see (Omelchenko et al., 2005; Makarova et al., 2007; Sghaier et al., 2007; Makarova and Daly, 2011) and references therein).

Presently, besides many genome projects of IRRP in progress (*e.g. Acinetobacter radioresistens*), many completely sequenced IR-resistant genomes are available on public genome databases (*e.g. Deinococcus proteolyticus* MRP (Liolios et al., 2010)) or were published very recently (*e.g. Deinococcus maricopensis* DSM21211 (Pukall et al., 2011)). However, completely sequenced IR-resistant genomes (Liolios et al., 2010), with published information regarding their IR resistance, are relatively limited in number and restricted in genera: *Deinococcus deserti* VCD115 (de Groot et al., 2005; de Groot et al., 2009; Baudet et al., 2010), *Deinococcus geothermalis* DSM 11300 (Makarova et al., 2007), *D. radiodurans* R_1 (White et al., 1999), two species of *Halobacterium* (*H. salinarum* R1 (Pfeiffer et al., 2008) and *Halobacterium* sp. NRC-1 (Ng et al., 2000)) (Ng et al., 2008), *Kineococcus radiotolerans* SRS30216 (Bagwell et al., 2008), *Rubrobacter xylanophilus* DSM 9941, *Methylobacterium radiotolerans* JCM 2831 (Liolios et al., 2010), three species of *Pyrococcus* (*P. abyssi* GE5 (Cohen et al., 2003), *P. furiosus* DSM 3638 (Maeder et al., 1999), and *P. horikoshii* OT3 (Kawarabayasi et al., 1998)), *Thermococcus gammatolerans* EJ3

(Jolivet et al., 2003a; Liolios et al., 2010), and *Truepera radiovictrix* DSM 17093 (Ivanova et al., 2011). In concordance with previous literature (Koonin, 2003), genes shared by the above-mentioned members of prokaryotic IR-resistant taxa based on TaxPlot available through the NCBI database (Sayers et al., 2011) suggest that the hypothesis of a common ancestor is quantitatively tenable. Qualitatively (Ouzounis et al., 2006), and in contrast to other phenotypes such as those characterized by (hyper)thermophily or pathogenecity, IR resistance does not have characteristic large genetic traits (mutagenesis cassettes, genomic islets (< 10 kilobase pairs (kb)) or fitness islands (> 10 kb), *etc.*) that are either correlated to IR resistance, specific to IRRP, or absent in IRSP. Hallmark genes correlated to IR resistance could be classified into four major evolutionary families on the basis of their mode of contribution to DNA repair (directly through interactions with DNA or indirectly by interactions without DNA) and their prokaryotic distribution:

- Family 1: Composed of genes assuming fundamental and direct functions related to DNA replication and repair (*e.g. polA*, *recA*) (Kim and Cox, 2002; Zahradka et al., 2006). Members of this family, or their orthologs, are present in all previously studied IRRP (Ouzounis et al., 2006; Sghaier et al., 2008). For instance, RecA protein is quintessential for the fidelity of repair of IR-induced DNA breaks and, consequently, for genome stability in *D. radiodurans* (Repar et al., 2010). In addition, the RecA mutant is among the most IR-sensitive mutants found in *D. radiodurans* (Moseley and Copland, 1975).
- Family 2: Containing genes that contribute directly to IR resistance (*e.g.* DNA nonhomologous end-joining complex) (Weller et al., 2002). Genes of this family are present in several IR-resistant lineages (Aravind and Koonin, 2001).
- Family 3: Comprising genes that contribute indirectly to IR resistance (*e.g.* superoxide dismutase, catalase) (Markillie et al., 1999). These genes are shared by some IRRP (Klotz and Loewen, 2003).
- Family 4: Containing genus- or species-specific genes that contribute directly or indirectly to IR resistance (*e.g. pprI* and *pprA* in *Deinococcus*) (Hua et al., 2003; Narumi et al., 2004). Interestingly, genes of this family enhance DNA repair abilities (Narumi et al., 2004) and regulation mechanisms through check points (Hua et al., 2003).

Previous work by Zahradka *et al.* revealed the relevant two-stage DNA repair process involving PolA and RecA DNA repair enzymes during recovery of *D. radiodurans* from IR (Zahradka et al., 2006). Moreover, the key steps and enzymes involved in ESDSA were identified (Galhardo and Rosenberg, 2009; Slade et al., 2009). Particularly, *polA* and *recA* homologs, belonging to Family 1 (see above), are found among all IRRP. Therefore, the proposal of an ancestral ESDSA repair process (Zahradka et al., 2006) is plausible from a comparative genomics perspective. Since ancestral proteins are reconstructable (Thornton, 2004), the above data suggest that ESDSA might shed light through complementation assays on the IR sensitivity or IR resistance of any node in a phylogenetic tree of PolA or RecA. For instance, a resurrected ancestral PolA protein might be used to complement IR-sensitive cells that are deficient in PolA and for which the wild-type is IR-resistant. The PolA-RecA-mediated repair process possesses the following important characteristics:

1. Functionally, its proteins (PolA and RecA) are important for IR resistance (DiRuggiero et al., 1997; Cox and Battista, 2005; Zahradka et al., 2006; Galhardo and Rosenberg, 2009; Slade et al., 2009; Repar et al., 2010).
2. Phylogenetically, it is a ubiquitous repair mechanism, and it is traced back to LUCA (DiRuggiero et al., 1999; Koonin, 2003; Ouzounis et al., 2006).

3. Evolutionarily, its informational proteins have not been subject to lateral gene transfer (Jain et al., 1999; Koonin, 2003; Ouzounis et al., 2006; Cohen et al., 2011).

The first stage of the two-stage DNA repair process involves a PolA-dependent ESDSA mechanism (Zahradka et al., 2006). This stage mainly requires a functional PolA enzyme and at least two genome copies that are broken at different positions. Knowing that IR-sensitive *D. radiodurans polA* mutants are fully complemented by expression of the *polA* gene from the relatively IR-sensitive *E. coli* (Gutman et al., 1994), and that many IRSP are polyploid (Daly and Minton, 1995), it is legitimate to propose that the first stage of the two-stage DNA repair process could be functional in IRSP. However, the possibility that some deinococcal hypothetical protein(s) or orphan(s) facilitates DNA synthesis by 'any' functional PolA must be seriously considered. This preparation of chromosomal fragments by hypothetical protein(s), albeit not demonstrated, might explain the delay of 1.5 hours in DNA synthesis in the wild-type (Zahradka et al., 2006) and is consistent with the presence of many species-specific proteins in *D. radiodurans*.

The second stage of the two-stage DNA repair process involves RecA-dependent crossovers in *D. radiodurans* (Zahradka et al., 2006), belonging to Mn-accumulating bacteria (Daly et al., 2004). In general, (1) ionic strength affects RecA binding preferential affinity to DNA in relation to single-stranded DNA or double-stranded DNA (Cazenave et al., 1983), and (2) Mn ions have possible effects on DNA structure (stabilization of the helix, neutralization of the negative charge of the phosphate backbone, prevention of DNA renaturation, *etc.*) (Polyanichko et al., 2004). Thus, it is legitimate at this point to assume that the *in vivo* affinity for DNA of 'any' RecA within *D. radiodurans* will differ from its *in vivo* affinity for DNA within an IR-sensitive cell like *E. coli*. Until more research is done, investigators presently agree that repair of DNA DSBs mediated by *recA*-like genes is an extremely active and distinct repair mechanism in *Deinococcus* and *Pyrococcus* (DiRuggiero et al., 1997; Kim and Cox, 2002; Zahradka et al., 2006; Sghaier et al., 2010).

Experimental support for the theory of an ancestral ESDSA repair process is needed. Having been discovered in *D. radiodurans* (Zahradka et al., 2006), an essential attribute of ESDSA is that its presence should also be testable experimentally in IR-resistant archaea.

A consideration of the evolution of IRRP in terms of phenotypic consequences representing genetic change would provide answers on how these organisms evolved. For example, comparative genomic surveys revealed that the radiation-desiccation resistance phenotype of *D. radiodurans* might have gradually evolved via cross-species gene transfer (Omelchenko et al., 2005). One aspect of this theory does seem correct: in contrast to *Pyrococcus*, *Deinococcus* clearly escaped with other Terrabacteria from a state of genetic shrinkage to "genetic gamble" in response to stress during land colonization (Battistuzzi et al., 2004). In this context, the "desiccation adaptation hypothesis" (Mattimore and Battista, 1996) suggests that the IR resistance of *D. radiodurans* is a consequence of its adaptation to desiccation. However, there is no genome-wide data or any experimental data to suggest that desiccation tolerance is antecedent to IR resistance. If this hypothesis is wrong, evolution of IRRP can be misinterpreted profoundly in numerous ways. Briefly, the data presented by Mattimore and Battista (Mattimore and Battista, 1996) only implied a strong positive correlation between these two phenotypes. In fact, a co-author of the "desiccation adaptation hypothesis" showed that inactivation of DRB0118, a constitutively expressed protein, greatly sensitizes *D. radiodurans* to desiccation, but not to IR (Battista et al., 2001). In addition, the ill-founded "desiccation adaptation hypothesis" (Mattimore and Battista, 1996) fails to explain the extreme IR resistance observed in several members of the domain

Archaea (*e.g. Pyrococcus*, *Thermococcus*). A recent *in vitro* investigation (Beblo et al., 2011) led to a definitive refutation of the "desiccation adaptation hypothesis" (Mattimore and Battista, 1996) and to an implicit vindication of the "radiation adaptation hypothesis" (Sghaier et al., 2007). In brief, it was demonstrated that desiccation-tolerant as well as desiccation-intolerant (hyper-) thermophilic archaea survived comparably high doses of IR (Beblo et al., 2011). In so far as other mechanisms of IR resistance are concerned, it is not surprising that the *Deinococcus* lineage does not share with *Pyrococcus* its five transcripts (DR0423, *ddrA*; DR0070, *ddrB*; DR0003, *ddrC*; DR0326, *ddrD*; DRA0346, *pprA*), most likely evolving in response to IR and desiccation (Tanaka et al., 2004). This network of five transcripts is *Deinococcus* lineage-specific. Similarly, a putative DNA-repair gene cluster of five conserved hypothetical genes in *P. furiosus* (PF0639, PF0640, PF0641, PF0642, PF0643), specifically induced by exposure to IR and probably involved in translesion synthesis, seems to be unique to thermophilic archaea and bacteria (Williams et al., 2007). Does this mean that this putative cluster is important for thermophily? The answer is probably no. One could highlight the fact that the mechanism that protects the DNA against thermal degradation does not prevent the formation of DNA breaks during irradiation (Gerard et al., 2001).

A corollary to all these analyses is the notion that there is a multiplicity of evolutionary and functional processes associated with IR resistance (Omelchenko et al., 2005; Makarova et al., 2007; Sghaier et al., 2007; Daly, 2010; Makarova and Daly, 2011; Slade and Radman, 2011). However, this integrative appraisal does not exclude the possibility of common processes among IRRP. Future analyses might consider more experimental and genomic data from a variety of IRRP in order to determine whether they possess a set of genes that would refute either the concept of convergent evolution or the idea of a common ancestor.

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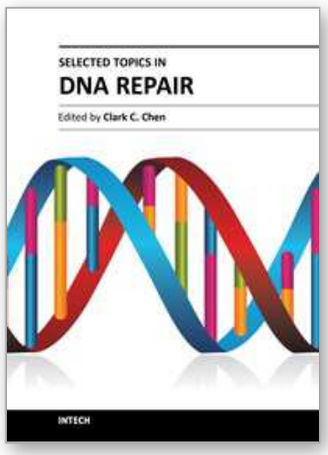

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This book is intended for students and scientists working in the field of DNA repair, focusing on a number of topics ranging from DNA damaging agents and mechanistic insights to methods in DNA repair and insights into therapeutic strategies. These topics demonstrate how scientific ideas are developed, tested, dialogued, and matured as it is meant to discuss key concepts in DNA repair. The book should serve as a supplementary text in courses and seminars as well as a general reference for biologists with an interest in DNA repair.

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